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(54) Title: BIODEGRADABLE POLYMER SYSTEMS

(57) Abstract: The rate of degradation of polymers and polymer blends containing (poly) lactic acid can be increased and controlled by the inclusion of up to 10% (typically less than 1%) by weight of specific additives such as lauric acid or a derivative thereof such as the anhydride.

Biodegradable Polymer Systems

This invention relates to biodegradable polymeric materials, particularly to bioresorbable materials and to artifacts made therefrom.

Poly (lactic acid), also commonly known as PLA has been widely used, either as the D-isomer or the mixed DL-form, for the manufacture of implant materials where bioresorbabilty is a required property. Although PLA is biodegradable it will normally take from 3 to 5 years to be fully resorbed. A further disadvantage is that although it takes 3 to 5 years to fully degrade the mechanical strength of implants made from poly (L-lactic acid)(PLLA) will be lost within a fifth of that time The *in vivo* degradation of PLA takes place predominately via an autocatalysed hydrolytic scission of the ester groups in the polymer chain according to the reaction:

$$\mathbf{\sim COO\sim + H_2O \xrightarrow{COOH} \sim COOH + HO\sim}$$

Attempts to increase the carboxylic acid functionality of the polymeric material and, hence, increase the rate of degradation of PLA have been reported in the literature *("Modification of the rates of chain cleavage of poly (ε-caprolactone) and related polyesters in the solid state",Journal of Controlled Release, 4, (1987) pp283-292.)* in which samples of PLA have been contacted with carboxyl group-containing materials such as oleic acid. No effect on the rate of degradation was reported. The effect of lactic acid monomer in PLA has also been investigated and reported (*"Effects of residual monomer on the degradation of DL-lactide polymer" Hyon, Jamshidi & Ikada, Polymer International, 46 (1998), pp196-202)*. However, it was found that the added monomer rapidly leached out of the polymer. Polymer blends containing 15 weight percent lactic acid exhibited a total weight loss of about 15% within the first week of a 10 week study and very little further loss in the remaining weeks.

In US Patent Specification No. 5 527 337 there is disclosed a biodegradeable stent formed from lactide polymers wherein, *inter alia,* an excipient such as ctric acid or fumaric acid can be incorporated during the polymer processing. Other additives which which can be used to accelerate stent degradation which are not acids themselves are also disclosed including the tertiary butyl ester of lauric acid and the ditertiary butyl ester of fumaric acid.

US Patent Specification No. 6 248 430 describes a laminate, for use in the manufacture of molded products for agricultural or civil engineering purposes. The laminate consists of a base layer comprising a lactic acid-based polymer having a degradation accelerator incorporated therein and a barrier layer which comprises a lactic acid based polymer having a lactide content of not more than 0.1% by weight, for the purpose of preventing the accelerator from leaking from the base polymer. The lactic acid-based polymer comprises a polyester made of polylactic acid component, lactic acid component dicarboxylic acid component, diol component and/or polyether component or a mixture thereof. Examples of materials useful as an accelerator include organic acids such as lactic, glyceric, tartaric, citric, lauric, stearic, oleic, succinic, adipic sebacic, benzoic and phthalic acids. The disclosure shows that the accelerators are incorporated during the polymer forming process.

Although it is known in the prior art to attempt to increase the carboxyl functionality by using acid based accelerators it has been a problem to retain such accelerators within the polymer mass for a sufficient period of time to allow control of the rate of degradation. The prior attempts to control degradation require either the use of physical barrier layers to retain the accelerator or the use of complex polymer systems.

We have now found that it is possible to control the rate of degradation of lactic acid polymers by homogeously blending certain

additives which are both fully miscible with PLA and will not leach out. The blending process is simple and results in stable polymer blends which can be readily thermoformed, such as by injection molding to form implantable medical devices which will both maintain their physical strength yet biodegrade in a predictable manner.

Thus in accordance with the present invention there is provided an implantable, biodegradable medical device formed from a homogeneous polymer blend comprising a poly lactic acid in admixture,in an amount of not more than 10% by weight of the polymer blend, with an additive which is an acid or a derivative thereof selected from the group consisting of hexanoic acid, octanoic acid, decanoic acid, lauric acid, myristic acid, crotonic acid, 4-pentenoic acid, 2-hexenoic acid, undecylenic acid, petroselenic acid, oleic acid, erucic acid, 2,4-hexadienoic acid, linoleic acid, linolenic acid, benzoic acid, hydrocinnamic acid, 4-isopropylbenzoic acid, ibuprofen, ricinoleic acid, adipic acid, suberic acid, phthalic acid, 2-bromolauric acid, 2,4-hydroxydodecanoic acid, monobutyrin, 2-hexyldecanoic acid, 2-butyloctanoic acid, 2-ethylhexanoic acid, 2-methylvaleric acid, 3-methylvaleric acid, 4-methylvaleric acid, 2-ethylbutyric acid, trans-beta-hydromuconic acid, isovaleric anhydride, hexanoic anhydride, decanoic anhydride, lauric anhydride, myristic anhydride, 4-pentenoic anhydride, oleic anhydride, linoleic anhydride, benzoic anhydride, poly(azelaic anhydride), 2-octen-1-yl succinic anhydride and phthalic anhydride.

The additive concentration is chosen such that it must be fully miscible with the polymer blend and should not leach out of the polymer.

As used herein the term "fully miscible" means that when an 0.5mm thick sheet of the polymer blend is visually inspected the sheet is either uniformly transparent or, if the sheet is opaque, the opacity is uniform.

As used herein the term "not leach out of the polymer" is defined such that when a thin (thickness <1mm) sample is immersed in an excess of PBS (Phosphate buffer solution), at least half of the added additive remains in the sample after 1 week.

Aptly the polymer blend will contain not more than 5%, more preferably not more than 2%, by weight of the additive and typically the blend will contain not more than 1% by weight of the additive. Preferred blends will contain not more than 2%, more preferably not more than 1%, by weight of the blend of lauric acid or a derivative thereof.

The amount of the additive chosen will also depend upon the rate of degradation desired. *In vivo* degradation occurs firstly by hydrolytic scission of the ester groups resulting in the formation of units of increasingly smaller molecular weight until only substantially lactic acid monomer remains. Thereafter, the lactic acid is metabolized and absorbed into the body. It is only in the last stages of degradation that mass loss occurs.

The mechanical properties of the implant are retained in the early stages of degradation, even though the molecular weight may decrease markedly. Eventually a critical molecular weight is reached and the implant will cease to have any useful mechanical strength yet will not have degraded sufficiently for resorption to occur.

We have found that a preferred additive for use in the invention is lauric acid. This may be employed as the acid *per se* or, if desired, as a derivative, for example as the anhydride.

By the use of the blends for the present invention not only may the total rate of degradation and resorption be controlled but it is possible to control the rate of degradation in order to optimize the mechanical properties. In many, surgical procedures, where the implant is required to provide temporary support until the condition has been treated by the body's own natural repair or rebuilding activity. When the support provided by the implant is no longer required it is often desirable that the strength of the implant be markedly reduced.

Thus in accordance with a further embodiment of the present invention there is provided an implantable, biodegradable medical device having predetermined strength retention comprising a homogeneous blend of a polylactic acid in admixture with an additive as hereinabove defined, in an amount, calculated as weight percent, based on the weight of the total polymer blend represented by the following equation:

$$\%additive = M_{nA} * 100 * \left\{ \left[\frac{Ln\left(\frac{M_{n0}}{M_{ns}}\right) - tk_1}{tk_2} \right]^2 - \frac{1}{M_{n0}} \right\}$$

where :-
M_{n0} = polymer initial molecular weight
M_{ns} = Mn at which the polymer looses strength
M_{nA} = molecular weight of the acid
t = Duration (weeks) that strength retention is required

k_1 = constant 1
k_2 = constant 2

The constants k_1 and k_2 are the slope and intercept of a graph of the degradation rate of a blend against the square root of the total number of COOH groups in the blend. The degradation rate of a blend is the slope of a graph of Ln(Mn) against degradation time in weeks.

The degradation rates of the additives employed as 2% by weight component in a polylactic acid blend in the present invention are shown in the following table:

Additive	Degradation rate
Hexanoic acid	-0.0565
Octanoic acid	-0.0448
Decanoic acid	-0.0472
Lauric acid	-0.0326
Myristic acid	-0.0281
Crotonic acid	-0.0489
4-Pentenoic acid	-0.0567
2-Hexenoic acid	-0.0713
Undecylenic acid	-0.07
Petroselenic acid	-0.0542
Oleic acid	-0.0442
Erucic acid	-0.0315
2,4-Hexadienoic acid	-0.0618
Linoleic acid	-0.0488
Linolenic acid	-0.0589
Benzoic acid	-0.0798
Hydrocinnamic acid	-0.0737
4-Isopropylbenzoic acid	-0.0728
Ibuprofen	-0.051
Ricinoleic acid	-0.061
Adipic acid	-0.0373
Suberic acid	-0.0311
Phthalic acid	-0.0855
2-Bromolauric acid	-0.0769
2,4-Hydroxydodecanoic acid	-0.0318

Monobutyrin	-0.0347
2-Hexyldecanoic acid	-0.0339
2-Butyloctanoic acid	-0.0467
2-Ethylhexanoic acid	-0.0473
2-Methylvaleric acid	-0.0411
3-Methylvaleric acid	-0.0587
4-Methylvaleric acid	-0.0553
2-Ethylbutyric acid	-0.053
Trans-beta-hydromuconic acid	-0.039
Isovaleric anhydride	-0.0628
Hexanoic anhydride	-0.0919
Decanoic anhydride	-0.0807
Lauric anhydride	-0.0698
Myristic anhydride	-0.0626
4-Pentenoic anhydride	-0.0888
Oleic anhydride	-0.0504
Linoleic anhydride	-0.0696
Benzoic anhydride	-0.0817
Poly(azelaic anhydride)	-0.0784
2-Octen-1-yl succinic anhydride	-0.1012
Phthalic anhydride	-0.0841

A further embodiment of the present invention provides the provision of an additive which not only will control the rate of degradation but will delay the onset of the degradation process. This delay may be achieved, aptly by the use of additives which are convertible to the acidic form of the additive. Suitable derivatives are acid anhydrides which will, in an *in vivo* environment hydrolyse to the corresponding acid. Preferred anhydrides include lauric anhydride and benzoic anhydride, in amounts of, aptly, not more than 5%, more aptly, not more than 2% and, typically, not more than 1% by weight of the polymer blend.

Thus specifically the present invention provides an implantable, biodegradable medical device having predetermined

strength retention comprising a homogeneous blend of a polylactic acid in admixture with lauric anhydride or benzoic anhydride in an amount, calculated as weight percent, based on the weight of the total polymer blend, represented by the following equation:

$$\%additive = M_{nA} * 100 * \left\{ \left[\frac{Ln\left(\frac{M_{n0}}{M_{ns}}\right) - tk_1}{tk_2} \right]^2 - \frac{1}{M_{n0}} \right\}$$

where $\mathbf{M_{n0}}$, $\mathbf{M_{ns}}$, $\mathbf{M_{nA}}$, $\mathbf{k_1}$ and $\mathbf{k_2}$ are as defined herein and $\mathbf{t}$ is the duration (weeks) that strength retention is required once onset of degradation has comenced

The polymeric component of the polymer blends useful for the invention essentially comprise a poly lactic acid. The poly lactic acid may be present as a homopolymer or as a co-polymer, for example a co-polymer of lactic acid and glycolic acid (known as PLA/PGA co-polymer). The polymer blend may also contain other polymeric components blended therewith. Thus the blend may, in addition to the additive, consist of a blend of polylactic acid, PLA/PGA co-polymer. Other examples of suitable blend include blends of PLA or PLA/PGA co-polymer either alone or in admixture with each other, together with hydroxy apatite.

The polymer blends used for the present invention may be produced by known processes such as solution blending wherein the additive is blended directly into a solution of a polymeric component comprising PLA in, for example, chloroform. The solution blend is then dried.

The thus formed solid blend may then be formed per se into the medical device of the invention, by known processes such as compression moulding or extrusion or into components, such as fibres which may be further processed to form devices in accordance with the present invention.

Alternatively, the blends may be further blended or ortherwise formulated with other materials to form medical devices in accordance with the invention. Thus the additive-containing blends may be utilized as the matrix component of a composite material which is then fabricated into a biodegradable medical device.

The medical devices of the invention are biodegradable and any implantable devices where temporary residence only is required. Examples of such devices include sutures, suture anchors, soft tissue anchors, interference screws, tissue engineering scaffolds, maxillo-facial plates, fracture fixation plates and rods.

The polymer blends themselves are believed to be novel compositions of matter.

Accordingly, the present invention further provides a polymer blend, useful for the manufacture of biodegradable medical devices comprising polylactic acid in admixture with an additive in an amount of not more than 10% by weight of the blend of at least one of hexanoic acid, octanoic acid, decanoic acid, lauric acid, myristic acid, crotonic acid, 4-pentenoic acid, 2-hexenoic acid, undecylenic acid, petroselenic acid, oleic acid, erucic acid, 2,4-hexadienoic acid, linoleic acid, linolenic acid, benzoic acid, hydrocinnamic acid, 4-isopropylbenzoic acid, ibuprofen, ricinoleic acid, adipic acid, suberic acid, phthalic acid, 2-bromolauric acid, 2,4-hydroxydodecanoic acid, monobutyrin, 2-hexyldecanoic acid, 2-butyloctanoic acid, 2-ethylhexanoic acid, 2-methylvaleric acid, 3-

methylvaleric acid, 4-methylvaleric acid, 2-ethylbutyric acid, trans-beta-hydromuconic acid, isovaleric anhydride, hexanoic anhydride, decanoic anhydride, lauric anhydride, myristic anhydride, 4-pentenoic anhydride, oleic anhydride, linoleic anhydride, benzoic anhydride, poly(azelaic anhydride), 2-octen-1-yl succinic anhydride or phthalic anhydride.

Aptly the blend will comprise not more than 5% by weight of the additive and preferably no more than 2% by weight of the additive.

The present invention will be illustrated by reference to the following and accompanying drawings.

Example 1

Blends of poly(L-lactic acid) containing lauric acid, in amounts respectively, 2% and 5% by weight of the blend, were prepared by first dry blending the solid materials and then solution blending the materials by roller mixing the solid mixture(10% by weight) with chloroform (90% by weight). After complete dissolution of the solids, the solutions were cast onto an open tray, left to dry (in a fume cupboard) at ambient temperature for 24 hours and dried for a further 24 hours under vacuum at ambient temperature. A control sample was also prepared by solution blending poly(L-lactic acid) alone with chloroform and drying the cast solution under the same conditions as the lauric acid-containing samples.

The dried cast films were then comminuted and approximately 10gm charges of the blends were compression moulded between two sheets of mould release sheets maintained 0.5mm apart. The charges were warmed for 5 minutes prior to moulding and fed into the mould at a temperature of 195°C ,

pressure of 100N over a period of 90 seconds to form sheets. The resultant sheets were observed to be transparent.

The sheets were cut into strips and subjected to simulated degradation by immersion in standard phosphate buffer solution (PBS), maintained at 37°C for 10 weeks.

During the ten week test period samples were analysed:

- o to determine molecular weight of the polymer blend(to measure the degree of degradation),
- o to determine the lauric acid in the polymer (to measure the degree of leaching of the lauric acid additive),
- o to determine the amount of Lactic acid in the PBS (to measure the amount of degradation products released into the PBS buffer).

The decrease in molecular weight is reported in Figure 1. The lauric acid remaining in the sample was determined by GC-MS. Samples were weighed (~50mg) and 2ml chloroform added. These were sonicated until the polymer dissolved. 20ml of diethyl ether was added to precipitate out the polymer, this was transferred to a 50ml volumetric and made to the mark with diethyl ether. An aliquot of the samples was vialled for analysis by GC-MS. The results for samples at weeks 0 and 10 are shown in Figure 2.

Samples of the PBS were also analysed by HPLC to determine the amount of lactic acid (to measure resorption potential). 31ml aliquots of the PBS were taken at each time interval and analysed under the following conditions:

Mobile Phase:	0.005N H_2SO_4 in water
Column:	Rezex 8μ 8% H. Organic Acids – 300 x 7.80 mm
Flow Rate:	0.6 ml/min
Injection Volume:	100μl
Column Temperature:	63°C
Wavelength:	210 nm
Runtime	20 min

The lactic acid content of the PBS is shown in Figure 3.

Example 2

Blends of poly(DL-lactic acid) containing lauric acid, in amounts respectively, 2% and 4% by weight of the blend, were prepared using the method described for Example 1.

The sheets were cut into strips and subjected to simulated degradation by immersion in standard phosphate buffer solution (PBS), maintained at 37°C for 8 weeks.

During the eight week test period samples were analysed:

- to determine molecular weight of the polymer blend(to measure the degree of degradation),
- Lactic acid (to measure the amount of degradation products released into the PBS buffer).

The decrease in molecular weight is reported in Figure 4, the lactic acid released into the PBS buffer in Figure 5.

Example 3

A blend of poly(L-lactic acid) containing 5% lauric acid was prepared by first dry blending the solid materials and then solution blending the materials by roller mixing the solid mixture (10% by weight) with chloroform (90% by weight). After complete dissolution of the solids, the solutions were cast onto an open tray, left to dry (in a fume cupboard) at ambient temperature for 24 hours and dried for a further 24 hours under vacuum at ambient temperature. A control sample was also prepared by solution blending poly(L-lactic acid) alone with chloroform and drying the cast solution under the same conditions as the lauric acid-containing samples.

The dried cast films were then comminuted and extruded at 180°C to produce rods with a diameter of approx 2mm. The resultant rods were observed to be slightly opaque, but uniform in colour.

The rods were then subjected to simulated degradation by immersion in standard phosphate buffer solution (PBS), maintained at 37°C for 8 weeks.

During the eight week test period samples of the billets were analysed:

- to determine molecular weight of the polymer blend(to measure the degree of degradation),
- to determine the tensile strength of the rods.

The decrease in molecular weight is reported in Figure 6. The tensile strength of the rods was measured using a gauge length of 40mm and a test speed of 10mm/min, the results are reported in Figure 7.

Example 4

A blend of poly(L-lactic acid) containing 1% lauric acid was prepared by first dry blending the solid materials and then extruding the mixture at 195°C. The subsequent polymer blend was then analysed to determine the lauric acid content, which was measured at 0.9%. The resultant rod material was observed to be transparent.

Example 5

Blends of poly(L-lactic acid) containing lauric anhydride, in amounts respectively, 2% and 5% by weight of the blend, were prepared by first dry blending the solid materials and then solution blending the materials by roller mixing the solid mixture (10% by weight) with chloroform (90% by weight). After complete dissolution of the solids, the solutions were cast onto an open tray, left to dry (in a fume cupboard) at ambient temperature for 24 hours and dried for a further 24 hours under vacuum at ambient temperature. A control sample was also prepared by solution blending poly(L-lactic acid) alone with chloroform and drying the cast solution under the same conditions as the lauric acid-containing samples.

The dried cast films were then comminuted and approximately 10gm charges of the blends were compression moulded between two sheets of mould release sheets maintained 0.5mm apart. The charges were warmed for 5 minutes prior to moulding and fed into the mould at a temperature of 195°C, pressure of 100N over a period of 90 seconds to form sheets. The resultant sheets were observed to be transparent.

The sheets were cut into strips and subjected to simulated degradation by immersion in standard phosphate buffer solution (PBS), maintained at 37°C for 8 weeks.

During the eight week test period samples of the sheets were analysed to determine molecular weight of the polymer blend(to measure the degree of degradation). The decrease in molecular weight is reported in Figure 8.

Example 6

The process of Example 5 was repeated using a blend of poly (L-lactic acid) containing 2% by weight benzoic acid anhydride. The reduction of molecular weight with time is shown in Figure 9.

The decrease in molecular weight over the twenty week test period showed that there was very little degradation (loss in molecular weight) within the first ten weeks

Example 7

The process of Example 1 was repeated to make blends of poly (L-lactic acid) containing 2% by weight of the following acids:

Phthalic acid
2-Hexanoic
4-Isopropylbenzoic acid
Hydrocinnamic acid
2-Bromolauric acid
Benzoic acid
Lauric acid
Undecylenic acid
2-4 Hexadienoic
PLA control

The results of a plot of molecular weight decreas with time is shown in Figure 10.

Example 8

The product of Example 4 , ie rods of a blend of poly (L-lactic acid) containing 0.9% by weight of Lauric acid, were cut up into short lengths (typically about 3mm). This material was then formed into an interference screw (for soft tissue anchorage) by injection moulding using an Arburg 270M All Rounder 500-90 machine with the following conditions:

Temp at nozzle = 224°C
Barrel Temp = 235°C
Injection pressure = 1500 bar

Mould temp = 18°C

The resultant moulded devices had filled the mould well and were transparent.

CLAIMS

1. An implantable, biodegradable medical device formed from a homogeneous polymer blend comprising a lactic acid polymer in admixture,in an amount of not more than 10% by weight of the polymer blend, with an additive which is an acid or a derivative thereof selected from the group consisting of hexanoic acid, octanoic acid, decanoic acid, lauric acid, myristic acid, crotonic acid, 4-pentenoic acid, 2-hexenoic acid, undecylenic acid, petroselenic acid, oleic acid, erucic acid, 2,4-hexadienoic acid, linoleic acid, linolenic acid, benzoic acid, hydrocinnamic acid, 4-isopropylbenzoic acid, ibuprofen, ricinoleic acid, adipic acid, suberic acid, phthalic acid, 2-bromolauric acid, 2,4-hydroxydodecanoic acid, monobutyrin, 2-hexyldecanoic acid, 2-butyloctanoic acid, 2-ethylhexanoic acid, 2-methylvaleric acid, 3-methylvaleric acid, 4-methylvaleric acid, 2-ethylbutyric acid, trans-beta-hydromuconic acid, isovaleric anhydride, hexanoic anhydride, decanoic anhydride, lauric anhydride, myristic anhydride, 4-pentenoic anhydride, oleic anhydride, linoleic anhydride, benzoic anhydride, poly(azelaic anhydride), 2-octen-1-yl succinic anhydride and phthalic anhydride.

2. An implantable, biodegradable medical device having predetermined strength retention comprising a homogeneous blend of a lactic acid polymer in admixture with an additive as hereinabove defined, in an amount, calculated as weight percent, based on the weight of the total polymer blend represented by the following equation:

$$\%additive = M_{nA} * 100 * \left\{ \left[\frac{Ln\left(\frac{M_{n0}}{M_{ns}}\right) - tk_1}{tk_2} \right]^2 - \frac{1}{M_{n0}} \right\}$$

where :-

M_{n0} = polymer initial molecular weight

M_{ns} = Mn at which the polymer looses strength

M_{nA} = molecular weight of the acid

t = Duration (weeks) that strength retention is required once the onset of degradation has commenced

K_1 = constant 1

K_2 = constant 2

3. A device as claimed in either claim 1 or claim 2 wherein the additive is lauric cid anhydride or benzoic acid anhydride.

4. A device as claimed in any one of the previous claims wherein the polymer blend contains not more than 2%, by weight of the additive .

5. A device as claimed in any one of the preceding claims wherein the lactic acid polymer is poly lactic acid

6. A device as claimed in any one of claims 1 to 5 wherein the lactic acid polymer is a copolymer with glycolic acid

7. A device as claimed in any one of the previous claims wherein the polymer blend comprises additional polymeric components.

8. A device as claimed in any one of the previous claims wherein the polymer blend is the matrix component of a composite material from which the device is formed.

9. A device as claimed in any one of the previous claims in the form of a suture, suture anchor, soft tissue anchor, interference screw, tissue engineering scaffold, maxial-facial plate, or a fracture fixation plate or rod.

10. A polymer blend, useful for the manufacture of biodegradable medical devices comprising polylactic acid in admixture with an additive in an amount of not more than 10% by weight of the blend of at least one of hexanoic acid, octanoic acid, decanoic acid, lauric acid, myristic acid, crotonic acid, 4-pentenoic acid, 2-hexenoic acid, undecylenic acid, petroselenic acid, oleic acid, erucic acid, 2,4-hexadienoic acid, linoleic acid, linolenic acid, benzoic acid, hydrocinnamic acid, 4-isopropylbenzoic acid, ibuprofen, ricinoleic acid, adipic acid, suberic acid, phthalic acid, 2-bromolauric acid, 2,4-hydroxydodecanoic acid, monobutyrin, 2-hexyldecanoic acid, 2-butyloctanoic acid, 2-ethylhexanoic acid, 2-methylvaleric acid, 3-methylvaleric acid, 4-methylvaleric acid, 2-ethylbutyric acid, trans-beta-hydromuconic acid, isovaleric anhydride, hexanoic anhydride, decanoic anhydride, lauric anhydride, myristic anhydride, 4-pentenoic anhydride, oleic anhydride, linoleic anhydride, benzoic anhydride, poly(azelaic anhydride), 2-octen-1-yl succinic anhydride or phthalic anhydride.

11. A blend was claimed in claim 10 comprising not more than 5% by weight of the additive.

12. A blend was claimed in claim 11 comprising no more than 2% by weight of the additive.

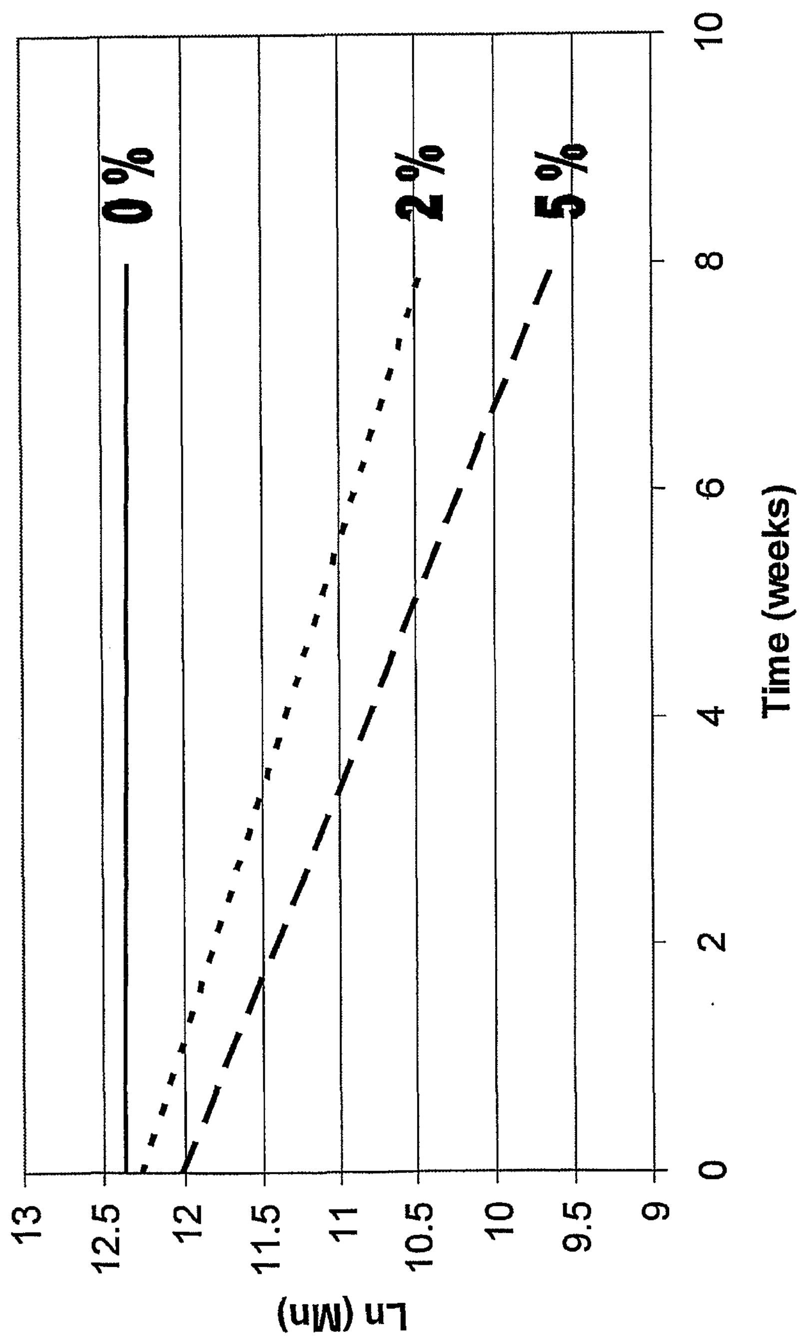

Figure 1

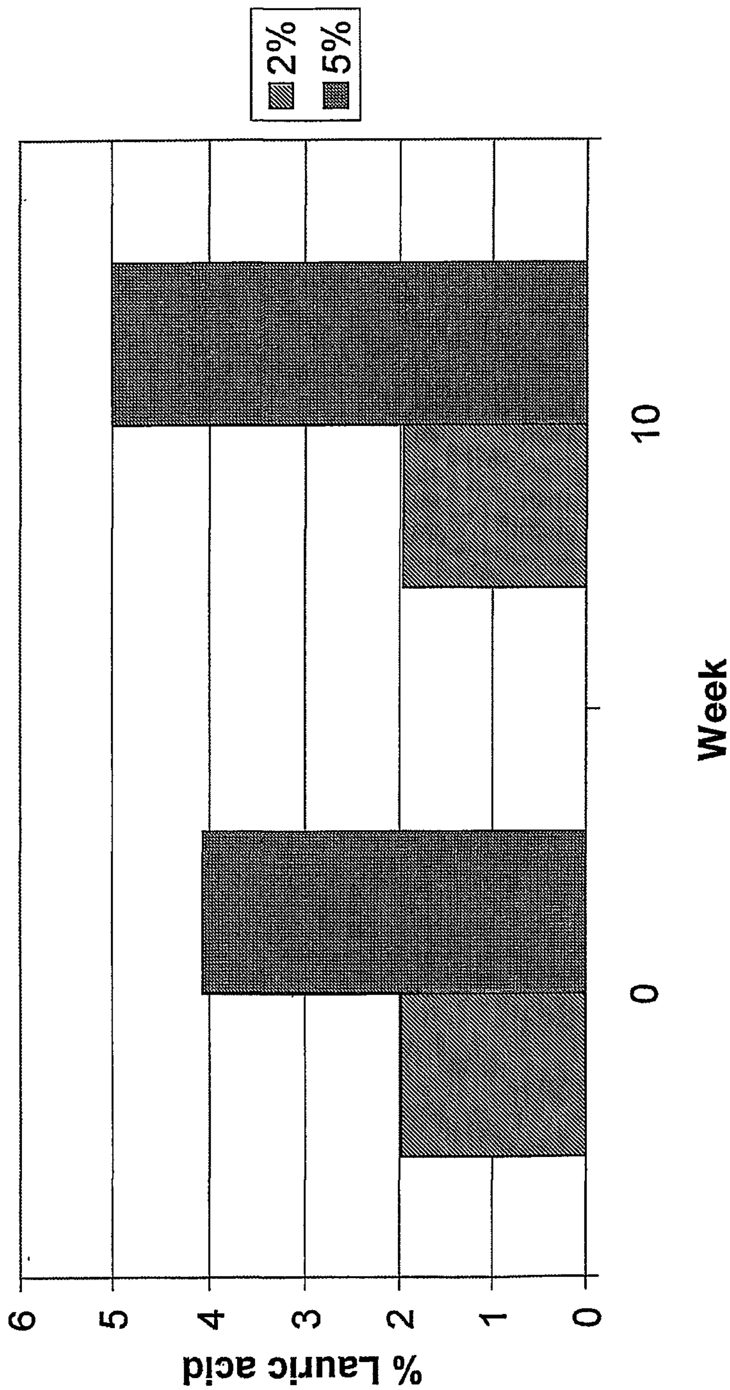

Figure 2

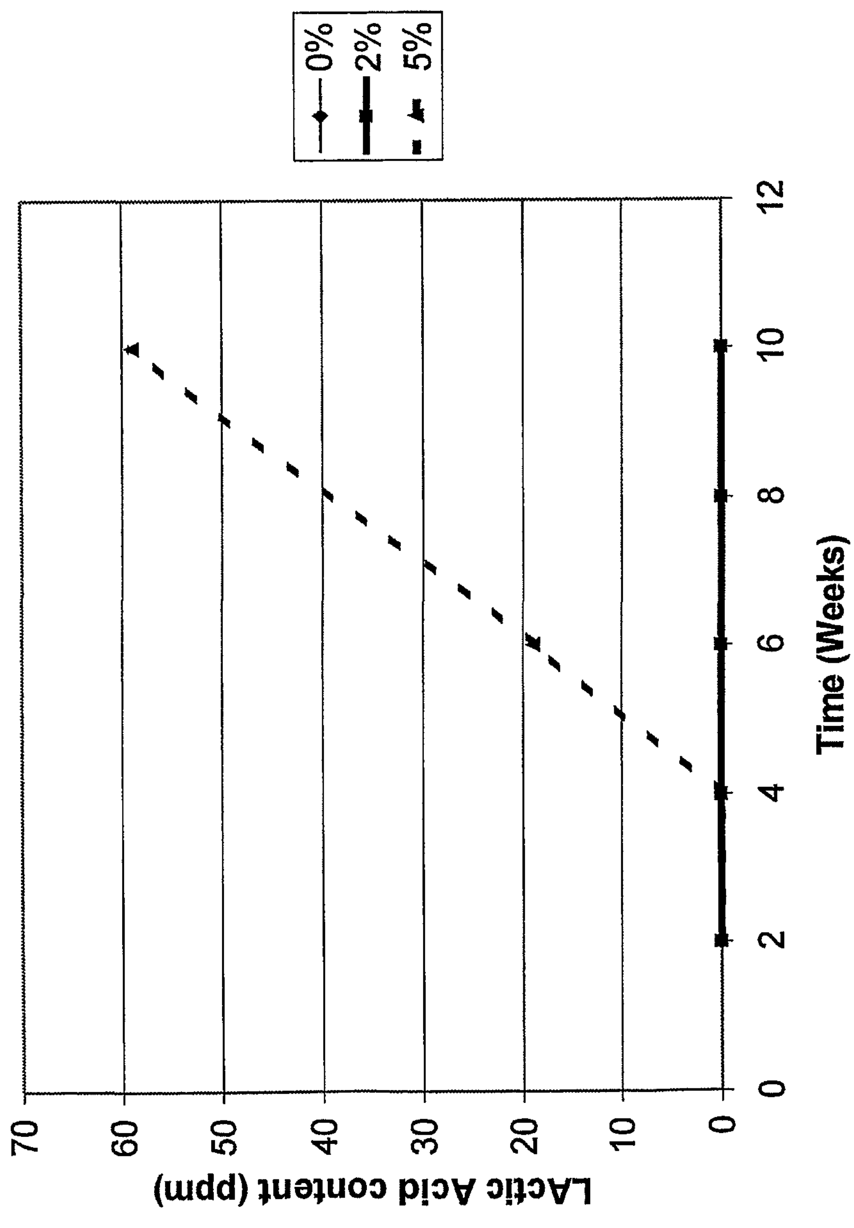
0%
2%
5%
Lactic Acid content (ppm)
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (Weeks)

Figure 3

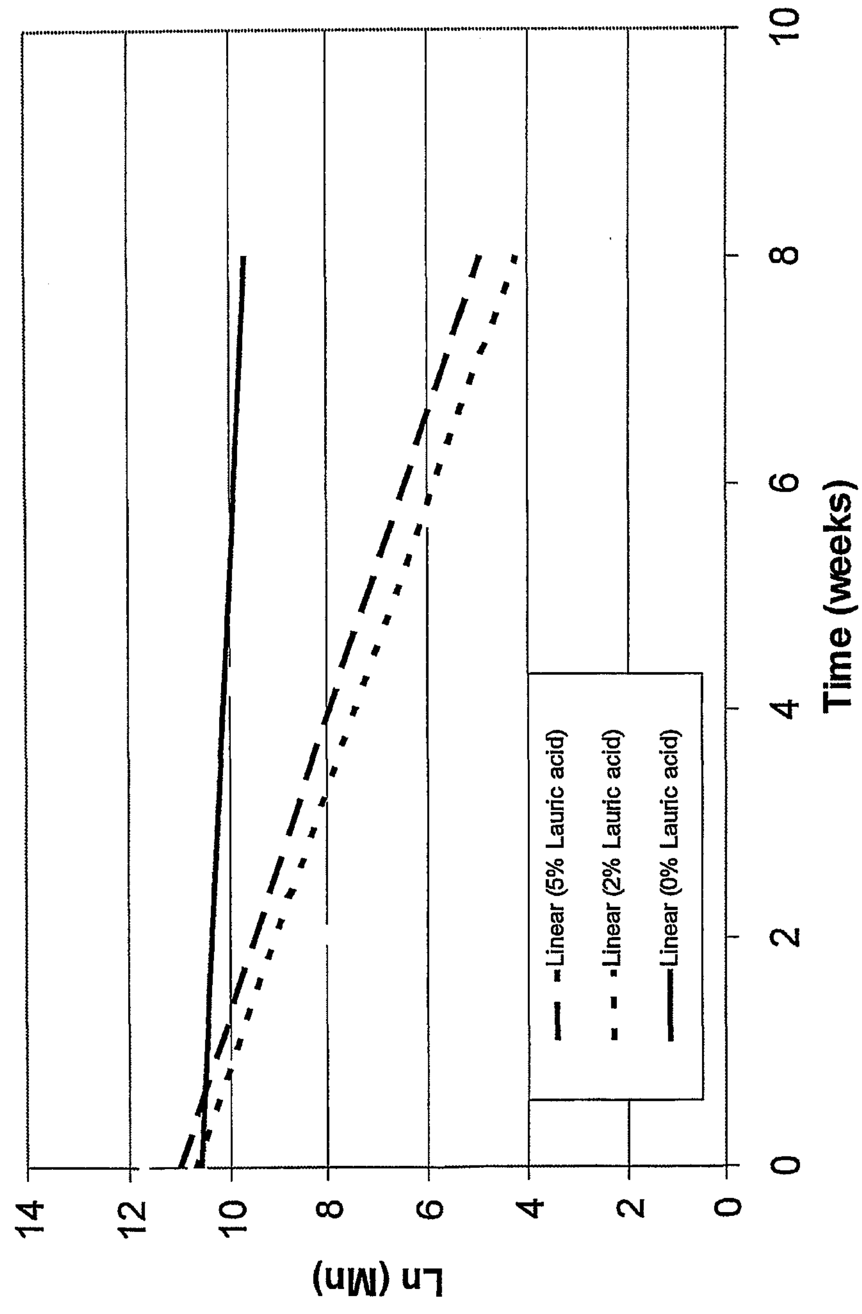
Ln (Mn)
14
12
10
8
6
4
2
0
Time (weeks)
0
2
4
6
8
10
Linear (5% Lauric acid)
Linear (2% Lauric acid)
Linear (0% Lauric acid)

Figure 4

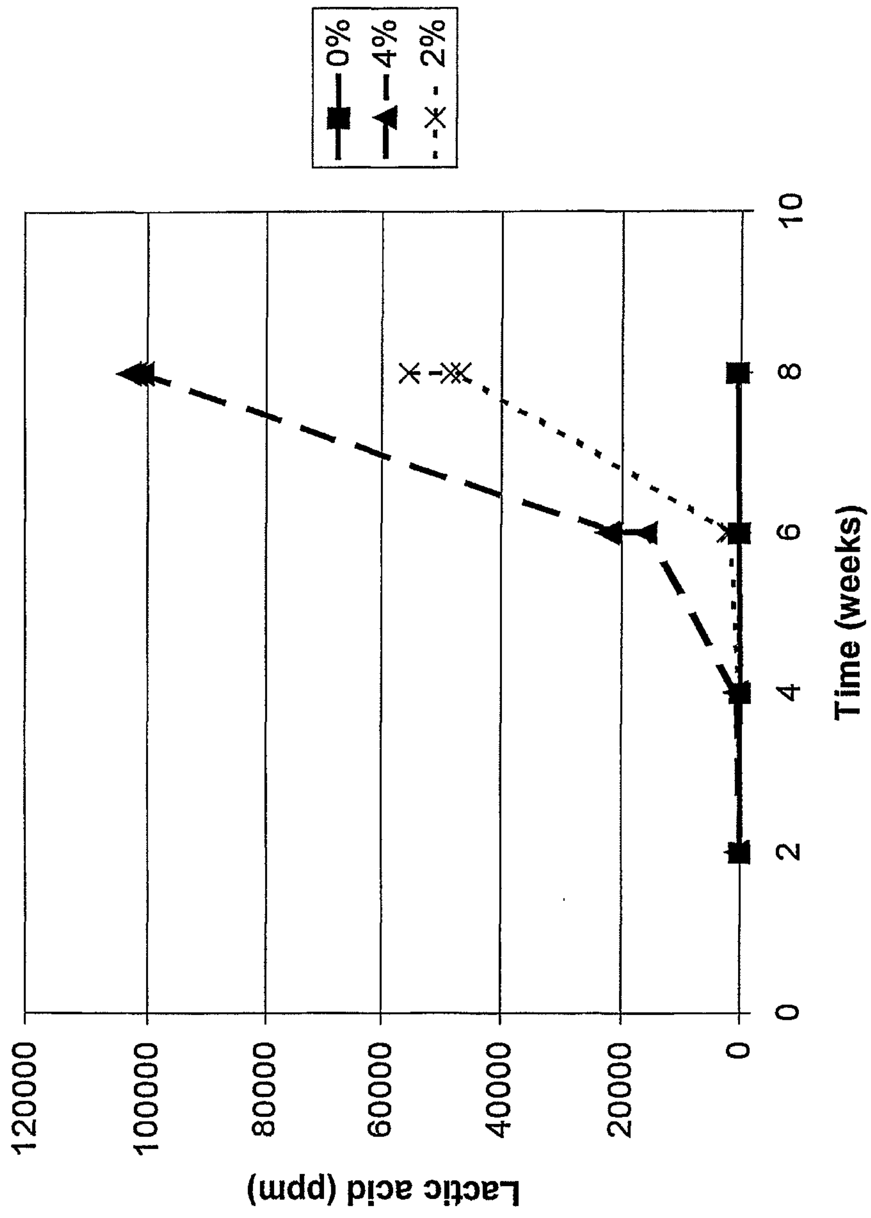
Lactic acid (ppm)
120000
100000
80000
60000
40000
20000
0
0
2
4
6
8
10
Time (weeks)
0%
4%
2%

Figure 5

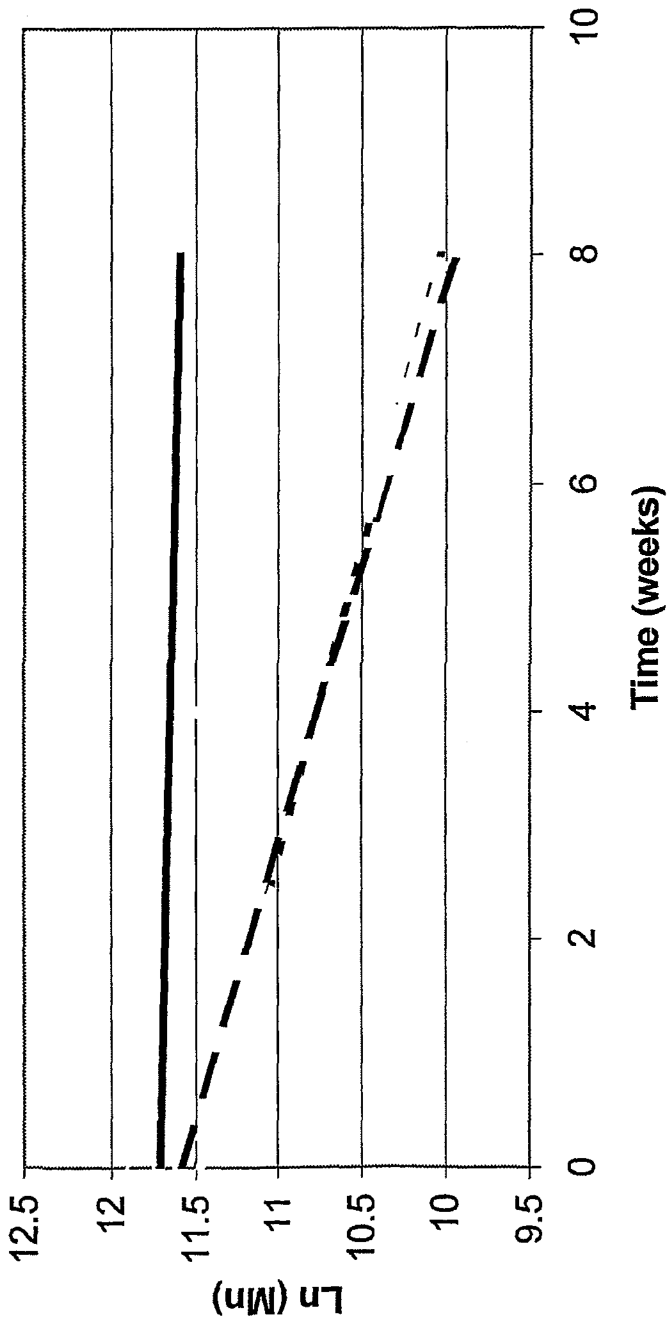

Figure 6

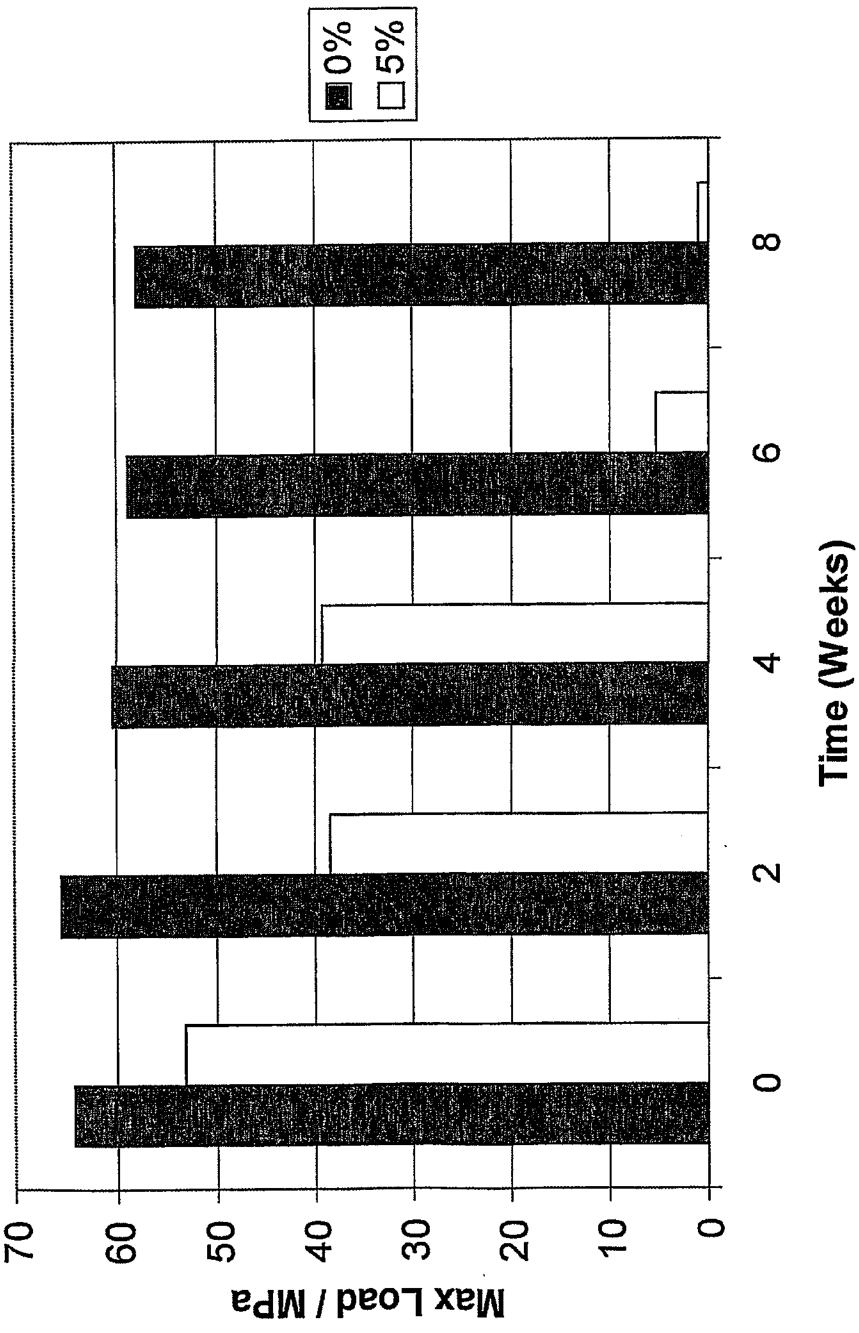

Figure 7

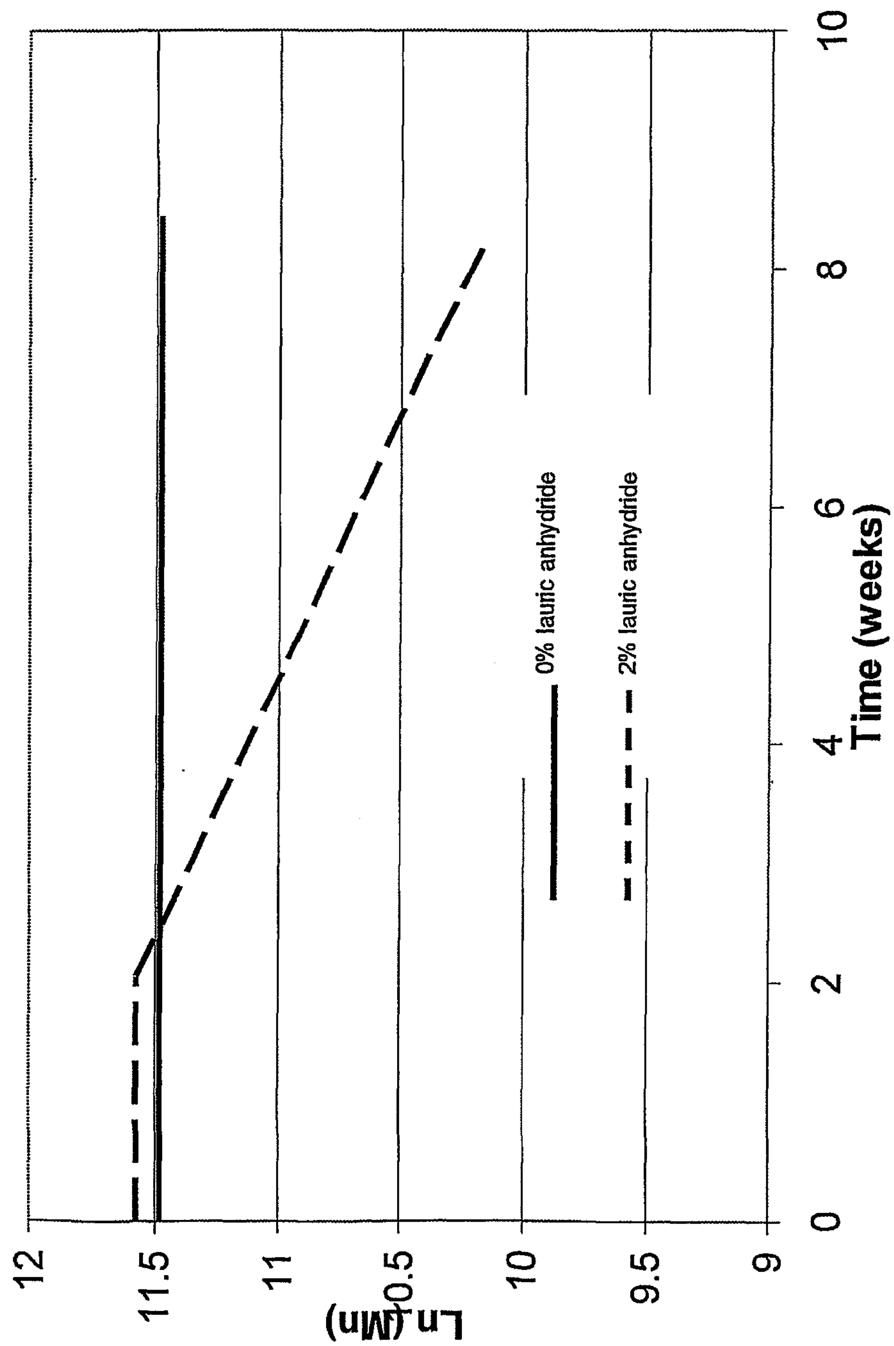
12
11.5
11
10.5
10
9.5
9
Ln (Mn)
0
2
4
6
8
10
Time (weeks)
0% lauric anhydride
2% lauric anhydride

Figure 8

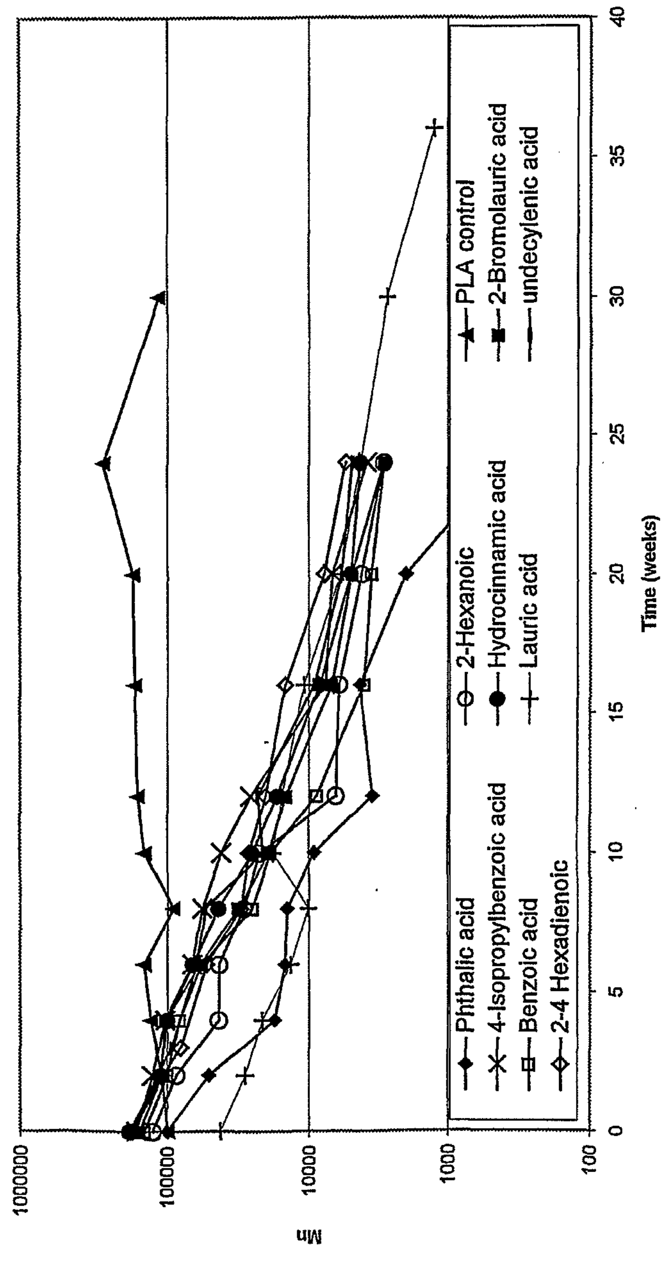
Mn
1000000
100000
10000
1000
100
0
5
10
15
20
25
30
35
40
Time (weeks)
Phthalic acid
4-Isopropylbenzoic acid
Benzoic acid
2-4 Hexadienoic
2-Hexanoic
Hydrocinnamic acid
Lauric acid
PLA control
2-Bromolauric acid
undecylenic acid

Figure 9

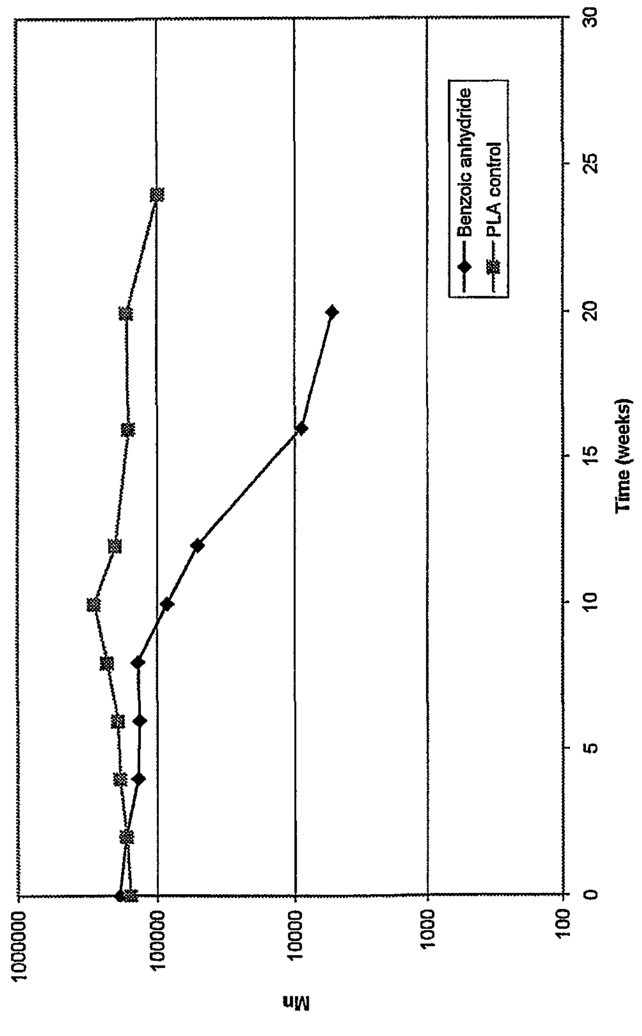
Benzoic anhydride
PLA control
Mn
1000000
100000
10000
1000
100
Time (weeks)
0
5
10
15
20
25
30

Figure 10

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L17/12 A61L27/14 A61L27/26 A61L27/44 A61L27/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 248 430 B1 (TOYODA AKIO ET AL) 19 June 2001 (2001-06-19) cited in the application column 3, line 10-43 column 4, line 3-16 column 8, line 12-39 column 9, line 11-18 table 1	1-12
X	US 5 527 337 A (MCELHANEY JAMES H ET AL) 18 June 1996 (1996-06-18) cited in the application column 3, line 35-56 column 8, line 60-65 column 9, line 11-17,36-50 column 11, line 17	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 2002	12/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Böhm, I

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 84 04311 A (HEXCEL CORP) 8 November 1984 (1984-11-08) claims -----	1

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03072

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 2 relates to a medical device comprising a lactic acid polymer in admixture with an additive defined (inter alia)

by reference to the following equation:

%additive= M(nA)*100*{'Ln(M(n0)/M(ns))/tk(2)!exp2 - 1/M(n0)}

The use of these equation in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the equation the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the technical feature of an implantable, biodegradable medical device having predetermined strength retention comprising a homogeneous blend of a lactic acid polymer in admixture with an additive according to claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03072

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
US 6248430	B1	19-06-2001	JP	2000117920	A	25-04-2000
US 5527337	A	18-06-1996	US	5059211	A	22-10-1991
			US	5306286	A	26-04-1994
			AU	653159	B2	22-09-1994
			AU	8001891	A	10-12-1991
			EP	0528993	A1	03-03-1993
			EP	0737453	A2	16-10-1996
			JP	5509008	T	16-12-1993
			WO	9117789	A1	28-11-1991
WO 8404311	A	08-11-1984	US	4643734	A	17-02-1987
			AT	45967	T	15-09-1989
			AU	569296	B2	28-01-1988
			AU	2826484	A	19-11-1984
			CA	1234247	A1	15-03-1988
			DE	3479585	D1	05-10-1989
			EP	0148852	A1	24-07-1985
			JP	7062066	B	05-07-1995
			JP	60501217	T	01-08-1985
			WO	8404311	A1	08-11-1984
			ZA	8403266	A	28-11-1984